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Economics of Insulin Device vs Conventional Vial and Syringe

Onur Baser · Jonathan Bouchard · Tony DeLuzio · Henry Henk · Mark Aagren

ABSTRACT

Introduction: Diabetes is difficult to manage and treatment involves significant lifestyle adjustments. Unlike the traditional method of insulin administration via the vial and syringe method, insulin pens might be perceived as less cumbersome and have potential to significantly increase patient adherence. **Methods:** Using “real world” data, we examined the differences in adherence and costs between diabetic patients using

an insulin FlexPen® (Novo Nordisk Inc, Princeton, NJ, USA) and those using traditional vial and syringe administration. Using a retrospective analysis of health insurance claims data between the years 2003 and 2008, we examined patients in the FlexPen cohort and analog vial cohort. Propensity score matching was used to match these cohorts ($n=532$ in each) according to baseline characteristics. **Results:** Adjusted mean medication possession ratio when switched to FlexPen improved by 22 percentage points versus 13 percentage points when continuing to use vials ($P=0.001$). Diabetes-related healthcare costs when switched to FlexPen versus continuing on to use vials (\$3970 vs. \$4838, respectively, $P=0.9368$) and total healthcare costs (\$13,214 vs. \$13,212, respectively, $P=0.9473$) were not statistically different. **Conclusion:** Without significant addition to the cost, insulin administration with FlexPen is associated with an improved adherence among patients who switched from vial-based insulin administration.

Keywords: adherence; costs; FlexPen; insulin; real world; syringe

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INTRODUCTION

Adherence to therapy is a major impact factor with respect to treatment success. For treatments such as those for type 2 diabetes, adherence to therapy can be perceived as particularly challenging as it is a lifelong chronic disease and patients may not feel the immediate consequences when skipping doses. Poor adherence to diabetes therapy, however, may have serious long-term and detrimental effects as patients are not in adequate glycemic control, which negatively affects risk of diabetes-related complications.¹ Landmark studies, such as the United Kingdom Prospective Diabetes Study (UKPDS), have shown that glycemic control as measured by glycated hemoglobin (HbA_{1c}) is a very important risk factor of complications, including blindness, amputations and cardiovascular disease.²

Type 2 diabetes imposes a significant burden on the US healthcare system. The American Diabetes Association estimates that 17.5 million Americans suffer from diabetes and that the total cost of diabetes in 2007 was \$174 billion, with \$116 billion direct costs to healthcare.³ Type 2 diabetes is considered to make up 90%-95% of all diabetes cases.⁴ Most of the burden and costs of diabetes originate from complications and treatment of complications (eg, >50% of costs are incurred in a hospital inpatient care setting).³

Thus, improvements in treatments and better adherence to treatments could benefit patients as well as healthcare plans and payers. Insulin therapy in particular can be of particular concern with respect to adherence because it is associated with hypoglycemic events, and due to the fact it is an injectable therapy, which might be perceived as inconvenient and/or difficult to administer by both patients and prescribers. Initiating and switching insulin therapy can be complicated for patients as well as prescribers,

as insulin therapy, whether used in vials or pens, demands extensive patient education and training. Treatments associated with discomfort such as injections, or risk of adverse events such as hypoglycemia, might keep some patients from faithfully following treatment guidelines, thereby reducing adherence.⁵

Poor adherence to long-term therapies compromises the effectiveness of treatment, making this a critical issue in population health from the perspective of both quality of life and health economics. It has been shown that poor adherence attenuates optimum clinical benefit.⁶ Therefore, medical innovations aimed at improving adherence might provide significant positive return investments through prevention of adverse health outcomes. Ease of use coupled with safety and dosing accuracy are ways to potentially improve adherence to therapy.^{7,8}

Insulin delivery by vial and syringe administration could be perceived as less convenient and less flexible for patients than pen-administered insulin for several reasons. The vial and syringe method requires complex dosing preparations and a longer training time, can be difficult to transport, uncomfortable for patients to self-inject, and might be associated with social stigma for some patients. Insulin delivery pens are generally easier to manage for patients and easier to teach how to use by healthcare professionals. Furthermore, pens are more discreet, easier to transport, provide better dosing accuracy, and feel less like a true injection, with less pain than the vial and syringe method.⁹

The present study was initiated, with the intention to analyze the impact on patient adherence, hypoglycemic events and treatment costs when switching from an insulin vial regimen to a FlexPen® (Novo Nordisk Inc, Princeton, NJ, USA) insulin pen regimen.

A study published in 2006 also set out to analyze the impact on adherence, hypoglycemia

and costs when switching from vial to FlexPen.¹⁰ In this study, it was reported that switching to FlexPen was indeed associated with improvements in adherence, which was accompanied by reductions in hypoglycemia as well as reductions in costs. The present study was conducted to analyze how adherence to therapy, insulin consumption, healthcare costs, and incidence of hypoglycemic events changed when patients were switched from vial therapy to FlexPen compared to a matched control cohort that did not switch but continued vial therapy.

MATERIALS AND METHODS

Data Sources and Study Population

Health Insurance Portability and Accountability Act (HIPAA)-compliant pharmacy and medical administrative claims data from a proprietary US health plan database was used

for this retrospective and longitudinal study. For 2008, data relating to approximately 14 million individuals is available. This data source is well validated, and represents one of the largest health plans in the US. These data were chosen because of their high validity and because they cover large numbers of patients across all parts of the US (see geographical split in Table 1).

The primary endpoint of the study was adherence as measured by adjusted medication possession ratio (MPR; see below for details). Secondary endpoints were insulin consumption, hypoglycemic events and healthcare costs.

Data were collected between January 1, 2003 and March 31, 2008. The database's study population included patients continuously enrolled in a commercial or Medicare health plan for at least 1 year. Patients had to have at least two insulin prescription fills during the pre-index period where at least one fill occurred during 1-6 month(s) before the index and at

Table 1. Baseline characteristics of the cohorts.

	FlexPen (<i>n</i> =532)	Vial (<i>n</i> =532)	<i>P</i> value
Age, years (mean±SD)	47.18±14.9	47.61±15.3	0.6730
Age group, <i>n</i> (%):			
0-17	28 (5.26)	18 (3.38)	0.1048
18-34	71 (13.35)	92 (17.29)	0.0665
35-44	112 (21.05)	92 (17.29)	0.1116
45-54	128 (24.06)	140 (26.32)	0.4076
55-64	151 (28.38)	128 (24.06)	0.0943
65-74	32 (6.02)	47 (8.83)	0.0750
75+	10 (1.88)	15 (2.82)	0.3173
Gender, <i>n</i> (%):			
Male	307 (57.71)	315 (59.21)	0.6184
Female	225 (42.29)	217 (40.79)	0.6184
Geographic region, <i>n</i> (%):			
Northeast	52 (9.77)	52 (9.77)	1.0000
North Central	170 (31.95)	185 (34.77)	0.3063
South	246 (46.24)	240 (45.11)	0.7021
West	64 (12.03)	55 (10.34)	0.3558
Unknown	0 (0.00)	0 (0.00)	1.0000

least one fill during the 7-12 months before the index.

Patients were excluded from the analysis:

(1) if they switched to another insulin than the index insulin or to another pen than FlexPen during the follow-up period; (2) if they had a fill for an insulin pen device, an insulin pump, or inhaled insulin in the pre- index period; or (3) if they had a diagnosis of gestational diabetes during the pre- or post- index period.

Patients were divided based on the two cohorts: FlexPen cohort and analog vial cohorts. We applied one-to-one matching to compare the outcomes of these cohorts. In Figure 1, a breakdown of the patient cohorts is shown.

Statistical Analysis

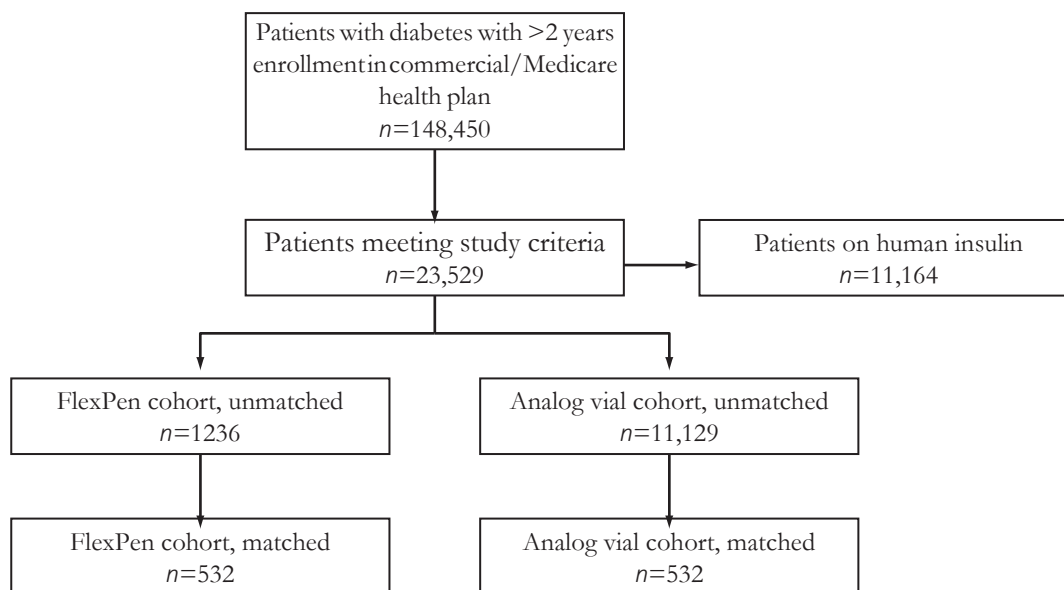
Baseline characteristics were compared between the patient cohorts and descriptive statistics were calculated as mean (\pm standard deviation) and percentages. Differences between

the cohorts were analyzed using the *t* test, Mann-Whitney *U* tests and chi-square test. Propensity score matching was applied to compare the risk-adjusted outcomes.

Propensity score matching is a technique that aims at adjusting for selection bias in nonexperimental, nonrandomized, and retrospective studies like the present one. By using propensity score matching, each patient in the FlexPen cohorts was “mirrored” by a patient with similar predefined characteristics in the cohorts not switching to FlexPen. The following characteristics were used to match: index year, diabetes type, age, age², gender, Charlson Comorbidity Index (CCI), CCI², geographic region, plan type, insulin consumption during baseline period, and commercial/Medicare.

Logistic regression was used to estimate propensity scores. Several interaction variables were attempted but they were not significant. Estimation power of the logistic model is determined with C statistics. We used mahalanobis, kernel, one-to-one, and radius

Figure 1. Flow chart of patients in the study.



matching techniques, and by following the guidelines set forth by Baser, determined that one-to-one matching created the best balance between the groups.¹¹ To eliminate further differences between the groups after propensity score matching, regression analysis followed over the matched sample.¹² Statistical analyses were performed using SAS v9.2 (SAS Institute, Cary, NC, USA) and STATA v10 (Stata Corp, College Station, TX, USA).

Adherence Measure

In this study, adherence to insulin therapy was measured among persistent patients (ie, patients who are not “dropping off” their insulin). Thus, adherence is a measure of how closely patients follow their medication regimen and not whether they remain on therapy. Traditionally, adherence is measured as the MPR, which is the total days’ supply of all prescriptions in the analysis period as registered by the pharmacy when the insulin prescription is filled, divided by number of days in the analysis period (ie, 365). Hence, unless a patient takes too much medication, MPR will be a number between 0 and 1, where 1 corresponds to the scenario where a patient adheres 100% to therapy.

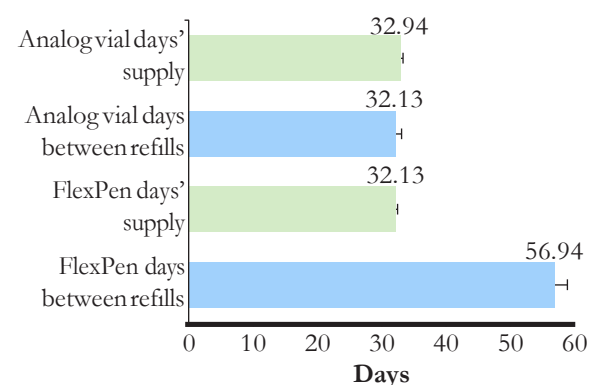
However, challenges exist when measuring adherence in a multidose treatment regimen such as insulin, as patients use different daily dosing dependent on, for example, body weight and progression of diabetes. Despite this fact, almost all prescriptions are dispensed with a 30-day supply documented by the pharmacy even if the patient has more insulin than ordered by the doctor after the 30-day period. Hence, patients might appear to be nonadherent as measured by MPR, even though they are in fact adherent to the instructions from their doctors. Furthermore, it can be a problem to compare the MPRs between treatments when package sizes are

different, which is the case with insulin in a vial versus insulin in a FlexPen. Vials are sold in packs of 1000 units while the FlexPen comes in packs of 1500 units, without any noticeable difference in days’ supply, as indicated in Figure 2.

To make adherence comparisons between the vials and the FlexPen feasible, it is necessary to adjust the MPR to account for the difference in package size. This adjusted MPR is calculated by using data based upon the actual gap between the days’ supply and the days to next refill for FlexPen and vials. Thus, the adjusted MPR for vials is calculated by multiplying the traditional MPR by (average days between prescription refills for patients using vials/average days’ supply for patients using vials). Likewise, the adjusted MPR for the FlexPen is calculated by multiplying the MPR by (average days between prescription refills for patients using FlexPen/average days’ supply for patients using FlexPen). In Figure 2, the discrepancy between days’ supply and the actual number of days to the next refill in the two cohorts is shown.

As shown in Figure 2 the average days’ supply and days between refills for vial patients are reasonably alike, but for FlexPen users the value for average days between refills is

Figure 2. Distribution of days supply of vials and FlexPen. Mean (including lower and upper 95% confidence intervals) days supplied and days between refills for FlexPen and vial users.



substantially longer than average days' supply. Hence, it is necessary to adjust the MPR as described above.

Insulin Consumption

Insulin daily average consumption (DACON), measured in insulin units, was computed from all prescription insulin fills based on the cohort. The total number of units dispensed was calculated as total milliliters dispensed for all prescriptions in the follow-up period (except the last fill in both the baseline and follow-up period) multiplied by 100, since there are 100 insulin units/mL. The total number of units dispensed was then divided by the number of days between index date and the date of last fill to calculate the average number of units of insulin per day.

Safety and Effectiveness

Only the hypoglycemic episodes obtained from the claims database that resulted in contact with healthcare professionals and were correctly coded with International Classification of Diseases, Ninth Revision: Clinical Modification (ICD-9-CM)

codes were registered and used in the analysis. In particular, we looked at hypoglycemic coma (ICD-9-CM: 251.0), other specified hypoglycemia (ICD-9-CM: 251.1), and unspecified hypoglycemia (ICD-9-CM: 251.2). Also included are the claims with ICD-9-CM code 250.8 (diabetes with other specified manifestations). The number of hypoglycemic episodes was compared pre- and post-index date.

Treatment effectiveness, preferably measured by changes in HbA_{1c} was not analyzed as this was not feasible. Even though laboratory test results, such as HbA_{1c}, are available for a subset of the data source used, there was not enough data available to keep an adequate number of patients with HbA_{1c} values in both the pre- and post-index periods in the study.

Healthcare Costs

Costs of treatment and healthcare costs in general were compared between the cohorts in the 12 months before and after the index date, ie, the first FlexPen prescription. Costs were calculated using actual patient claims and, thus, represent the true reflection of healthcare use in the matched cohorts.

Table 2. Insulin consumption and medication possession ratio.

	Vial to FlexPen (mean±SD)	Analog vials (mean±SD)	P value
12-month pre-index period			
MPR	0.52±0.27	0.52±0.24	0.7432
DACON	42.13±58.34	42.64±26.82	0.0565
12-month post-index period			
MPR*	0.55±0.31	0.60±0.30	0.0082
DACON	46.27±40.13	45.11±27.51	0.9641

Pre-index vial to FlexPen data are from patients who were using vial and syringe during the pre-index period, after which they switched to Flexpen. Their pre-index data reflect their vial and syringe baseline data.

*FlexPen post-index MPR is based on a pack size with 50% more insulin and with no noticeable difference in prescription days' supply (as seen in Figure 3).

DACON=insulin daily average consumption; MPR=medication possession ratio.

RESULTS

Baseline characteristics are summarized for the two cohorts of each database in Table 1. Since the FlexPen and vial cohorts were matched, the cohorts are reasonably alike and there were no statistical differences between the characteristics of the cohorts.

Daily consumption of insulin units and adherence to therapy pre- and post-index date are shown in Table 2. FlexPen users tended to increase their insulin usage more than the control group, ie, the patients continuing the vial/syringe therapy. The increase in dose was statistically significant ($P=0.0299$). An increase in consumption might be an indication of improved adherence, as better adherence within the same dosing regimen will lead to observed higher consumption because of a reduction of skipped/missed doses.

MPR improved between pre- and post-index for both cohorts. It is important to emphasize that MPR would be expected to decrease in the FlexPen cohorts without the days to next refill adjustment described earlier, because the pack in which it is sold contains 50% more units, and prescription days' supply does not differ between vials and FlexPen, as shown in Figure 2.

The adjusted MPR, controlling for the difference in pack size as well as patient

baseline characteristics, showed that patients switching to FlexPen markedly improved adherence compared to the control group. As can be seen in Table 3, the patient level and adjusted mean MPR when switched to FlexPen improved by 0.22 versus 0.13 when continuing to use vials ($P=0.001$).

Hypoglycemic events are shown in Figure 3.

The numbers of hypoglycemic events in both pre- and post-index periods were relatively small, and no statistical differences could be detected.

The cost of diabetes treatment and other healthcare costs are shown in Table 4. It can be seen that despite higher prescription costs in the FlexPen cohort, most likely due to higher acquisition costs of FlexPen versus vials, diabetes-related healthcare costs and total healthcare cost were not statistically different in the post-index period.

Figure 3. Hypoglycemic events pre- and post-index.

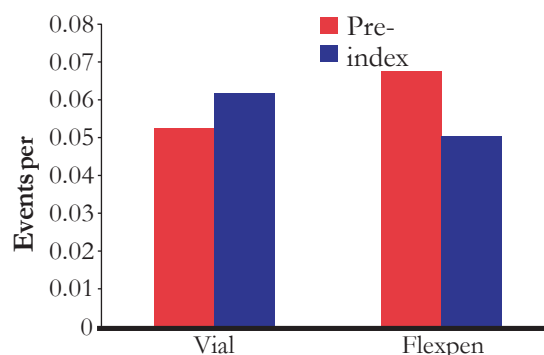


Table 3. Change in adjusted adherence.

	Vial to FlexPen (mean±SD)	Analog vials (mean±SD)	P value
Change			
Adjusted MPR	0.22±0.01	0.13±0.36	0.0011
DACON	3.27±0.85	2.18±0.65	0.001

Change is defined as the difference on a patient level from the pre-index period and the post-index period (post-index value minus pre-index value). Adjusted change in MPR is controlled for difference in pack sizes as well as baseline differences in demographic and clinical factors (see Materials and Methods section).

DACON=insulin daily average consumption; MPR=medication possession ratio.

Table 4. Costs of healthcare usage pre- and post-index.

	Vial to FlexPen (mean±SD)	Analog vials (mean±SD)	<i>P</i> value
12-month pre-index period			
Total healthcare costs	13,983±31,596	11,977±20,198	0.8238
Prescription costs	4328±5428	4582±4565	0.0455
All medical costs	9655±30,432	7396±18,250	0.4545
Diabetes-related medical costs	5241±19,009	3868±12,876	0.0107
12-month post-index period			
Total healthcare costs	13,214±23,917	13,212±26,570	0.9473
Prescription costs	5414± 7330	4790 ±4577	0.0802
All medical costs	7800±22,282	8421±24,509	0.2789
Diabetes-related medical costs	3970±12,851	4838±18,221	0.9368

Pre-index vial to FlexPen data are from patients who were using vial and syringe during the pre-index period, after which they switched to FlexPen. Their pre-index data reflects their vial and syringe baseline data.

DISCUSSION

The data analyzed as part of this study, based on healthcare claims, suggest that switching from insulin administration with vial and syringe to FlexPen administration is associated with improvement in adherence, when measured as adjusted MPR, and increased insulin consumption. Across both cohorts, insulin consumption increased from the pre- and post-index periods.

This is not surprising, as most patients will need more insulin over time to maintain glycemic control. It is important to remember that only patients who persisted with therapy were included, and therefore all patients probably tolerated treatment and benefited from it, which could be the reason for these dose increases. Any improvement of adherence is desirable, as treatment effects are dependent on patient adherence and, thus, impact the chance of treatment success.¹³

As stated in the Materials and Methods section, MPR is difficult to interpret when dealing with multidose regimens such as insulin, and therefore it is not sensible to make

conclusions based on the absolute value of the MPR (eg, that a patient with an MPR of 0.8 is more adherent to therapy than a patient with an MPR of 0.7). This does not mean, however, that comparisons of the changes in average MPR cannot be made, although they need be adjusted for the difference in pack sizes between FlexPen and vials. Even if interpersonal comparisons are problematic, intrapersonal comparisons, as undertaken in this study, are both reasonable and relevant.

The speculated and potential benefits of pen therapy, as provided by (among others) the FlexPen, include ease of administration and other convenience parameters. It is possible that these convenience aspects may contribute to the observed improved adherence in this study when patients are switched to FlexPen from vial therapy. FlexPen, and insulin pens in general, are in most cases priced higher on a unit-to-unit basis compared to insulin in vials.

This is also reflected in the results of this study, which shows that prescription costs, which were statistically significantly higher in the pre-index period, increase even though these are not statistically different in the post-

index period. Pre-index diabetes-related medical costs were statistically significantly higher among patients that switched to FlexPen, but no statistical difference was found in the post-index period. Also, overall healthcare costs did not significantly differ between patients who switched to FlexPen and patients who continued using vials (the matched control group).

Whether any impact of improved adherence can actually be seen in the short-term, which is the scope of the present analysis, is doubtful. Hence, it is probably not realistic to expect any major savings in medical service usage arising from improved adherence over the 12-month period applied here.

Insulin analogs have been shown in randomized clinical trials to be associated with fewer hypoglycemic events compared to human insulins.^{14,15} It appears from the present study, however nonsignificant, that the patients switched from vial and syringe to FlexPen had a higher risk of hypoglycemic events before switching to FlexPen, and lower risk after the switch; however, this was not statistically significant either. Using claims databases to analyze the incidence and full economic burden of hypoglycemic events provides unique challenges. In order to be measured in claims data, the hypoglycemic event would require contact with a healthcare professional. Secondly, the event would have to be documented on a medical claim, using the appropriate ICD-9-CM diagnostic code. Obviously, only the most serious hypoglycemic event cases result in contacts with healthcare professionals and therefore the incidence seen in analyses like this one are much lower than for example, incidences in clinical trials or survey data. This under-reporting means that even though there appears to be a difference between the cohorts, the numbers are too small to show any statistical significance. In general, the analyzed data do not suggest any

particular pattern with respect to hypoglycemic events before and after switching to the FlexPen, other than maybe that patients suffered from more events before they switched compared to patients who continued with vial therapy and fewer events after index. This was, however, not a statistically significant finding.

As previously mentioned, a study published in 2006 also set out to investigate the association between FlexPen use and adherence, costs and hypoglycemic events.¹⁰ However, the results of the present study cannot be directly compared with the aforementioned previous research since the methods are somewhat different. Even though both studies are pre- and post-index comparisons, the most noticeable difference is that the present study is a case-control analysis where patients switching to the FlexPen are compared to a matched cohort of patients. The Lee et al.¹⁰ study reported improved adherence, lower incidence of hypoglycemic events, and a reduction in overall healthcare costs when patients switched from vial to FlexPen administration. In another study among Medicaid-enrolled patients, initiation of insulin with pens was associated with less healthcare usage compared to patients initiated with vial and syringe.¹⁶ The data source analyzed in the present study confirms improvement of adherence when comparing to a matched cohort of vial users. The results show that adherence among persistent patients improves despite the administration device (ie, adherence improves in both cohorts). However, adherence improves significantly more among patients who switched to FlexPen administration. With respect to hypoglycemic events, the incidence numbers found in this study were very small and hence it was not possible to draw any conclusions on this topic. Regarding healthcare costs, which were shown to be reduced in the Lee et al. study, there is nothing in the present study that suggests any

difference in healthcare usage costs between FlexPen and vials users.

Several limitations of retrospective database analyses, and claims data in particular, should be noted. First and foremost, this is nonrandomized data and, consequently, there is potential selection bias in the data. This study, however, adjusts for this by using the matched cohort case-control approach and by adjusting adherence for baseline characteristics, but this does not rule out selection bias completely as there is no knowledge of the exact reason why patients switched insulin administration vehicle. Another important caveat is the calculation and interpretation of the MPR. As stated above, interpretations of absolute values of MPR must be made with extreme caution, as prescription days' supply does not necessarily reflect the expected time period that it is intended to fill. Furthermore, insulin usage as captured by claims data can be affected by, for example, wastage, and this cannot be adjusted for. However, there is no reason to suspect that the cohorts should be different in these matters, and emphasis of MPR should be put on the relative and pack size-adjusted differences.

CONCLUSIONS

This study has shown that insulin administration with FlexPen is associated with an improved adherence among patients who switch from vial-based insulin administration. This is based on an analysis of a data source using case-control analytics between cohorts that were matched for propensity score to control for selection bias.

This study also investigated the impact on incidence of hypoglycemic events as well as healthcare costs when patients switched to the FlexPen. However, hypoglycemic events as reported in claims databases are too sparse

to make any firm and statistically significant conclusions, but a trend towards improvements when patients were switched to the FlexPen was observed. Even though the FlexPen is associated with higher acquisition costs, this study showed that there was no difference with respect to overall healthcare costs.

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